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Diastereoselective nickel-catalyzed reductive couplings of aminoaldehydes and alkynylsilanes: application to the synthesis of D-*erythro*-sphingosine

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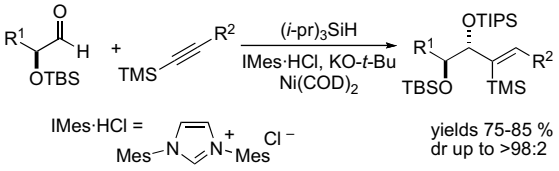
ABSTRACT

A strategy for the nickel-catalyzed reductive coupling of α-aminoaldehydes with silyl alkynes has been developed. The process proceeds with exceptional regiocontrol and diastereoselectivity. A variety of protected serinal derivatives were examined, and Garner aldehyde afforded the highest chemical yields of an easily deprotected coupling product. Use of a C-15 alkyne allowed a direct and efficient synthesis of D-*erythro*-sphingosine. With this silyl alkyne of interest, coupling reactions were most efficient when trace water was employed with THF as solvent. Using this procedure, D-*erythro*-sphingosine was prepared by a short sequence, wherein the alkene stereochemistry, C-3 stereocenter, and the C-3–C-4 carbon–carbon bond were all efficiently installed by the key nickel-catalyzed coupling process.

1. Introduction

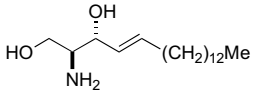
The reductive coupling of aldehydes and alkynes has been extensively developed as an entry to stereodefined allylic alcohols.[1] Numerous variants have been developed that involve alteration of the transition metal, ligand, or reducing agent.[2] In processes that involve nickel catalysis, both phosphine[3] and *N*-heterocyclic carbene ligands[4] and organosilane, organoborane, and organozinc reducing agents have been employed. In addition to extensive studies in the generation of racemic products, both enantioselective[5] and diastereoselective[6–8] processes have been developed. Highly diastereoselective processes have been illustrated involving chiral ynals in intramolecular variants[6] as well as chiral aldehydes[7] or chiral alkynes[8] in intermolecular variants.

A pair of recent reports illustrated that α-alkoxy and α-silyloxy aldehydes were effective participants in diastereoselective reductive couplings with various alkynes.[7] Our contribution illustrated that couplings of α-silyloxy aldehydes were most selective with silyl alkynes.[7b] In this prior report, we illustrated that a range of substitution patterns were accessible to generate functionalized *anti*-1,2-diols by this procedure. The best diastereselectivities and chemical yields were accessed when unbranched aldehyde and alkyne substrates were employed (Eq. 1).



(1)

In order to expand the scope and utility of this highly diastereoselective process, we anticipated that α-aminoaldehydes might be similarly effective in the coupling process. In addition to providing general access to stereodefined unsaturated amino alcohols, a method involving aminoaldehydes could additionally be applied in a direct entry to compounds of the sphingosine class.[9] While possessing the *anti*-amino alcohol structural motif that could be directly accessed by an aminoaldehyde alkyne reductive coupling, D-*erythro*-sphingosine (Scheme 1) has been the target of many synthetic approaches.[10] Despite the many impressive advances that have been made, assembly of the core structure by a single reductive operation involving an aldehyde and alkyne, while avoiding the stoichiometric generation of a reactive vinyl organometallic reagent, has not been previously realized. With these goals in mind, this report details an examination of the efficiency of reductive couplings of aminoaldehydes with alkynes as well as application of the method in the synthesis of D-*erythro*-sphingosine (Scheme 1).



Scheme 1. D-*erythro*-Sphingosine.

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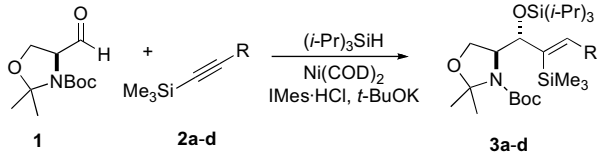
2. Results and discussion

Among many known protecting groups for α-amino aldehydes, Garner aldehyde **1** is particularly attractive from the standpoints of ease of chemical synthesis and purification, resistance to epimerization, and effectiveness in promoting highly diastereoselective transformations.[11] In fact, several of the most efficient syntheses of sphingosine have relied upon diastereoselective additions of either vinyl organometallic reagents or acetylide nucleophiles to this aldehyde. We therefore envisioned that the direct catalytic reductive coupling of an alkyne with this aldehyde would provide an attractive entry to stereodefined *anti*-1,2-aminoalcohols related to the core structure of sphingosine.

We initially examined the additions of silylalkynes **2a–c** with Garner aldehyde **1**, and were pleased to find that the procedure initially developed for diastereoselective additions to α-silyloxy-aldehydes[7b] was highly effective for additions to aldehyde **1** (Table 1). In these three examples, good chemical yields (68–80% yield) were observed, and only the *anti*-diastereomer with the *Z*-alkene was observed in the crude reaction mixtures (>95:5 dr, >95:5 *Z*/*E*). With these highly encouraging early results, we examined the couplings of the long-chain silyl alkyne **2d**, which would directly afford the core structure of D-*erythro*-sphingosine. However, although stereoselectivities were high, much lower chemical efficiency was observed than seen with the simpler silyl alkynes **2a–c**.

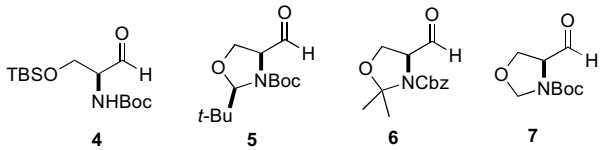
Table 1
Additions to Garner aldehyde **1**



1 **2a-d** **3a-d**

Entry	R	Product (yield)	dr
1	CH_3 (**2a**)	**3a** (78%)	>95:5
2	C_6H_5 (**2b**)	**3b** (80%)	>95:5
3	$(CH_2)_3CH_3$ (**2c**)	**3c** (68%)	>95:5
4	$(CH_2)_{12}CH_3$ (**2d**)	**3d** (18%)	>95:5

Whereas the reasons for the poor efficiency of couplings of alkyne **2d** with **1** are unclear, we anticipated that chemical efficiencies may be improved with alternate protecting groups for the α-amino-β-alkoxy aldehyde of interest. We therefore examined couplings of aldehydes **4–7** (Scheme 2), using the key silyl alkyne **2d** as the coupling partner. While couplings of **2d** with aldehydes **4–6** were very low yielding, chemical efficiencies with aldehyde **7** were much improved. Using aldehyde **7**, reductive couplings using alkynes **2a–d** were again examined, and all four examples now proceeded with similarly good chemical efficiencies and with outstanding stereocontrol to produce compounds **8a–d** (Table 2).

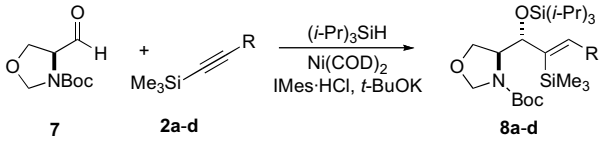


4 **5** **6** **7**

Scheme 2. Alternate protected aminoaldehydes.

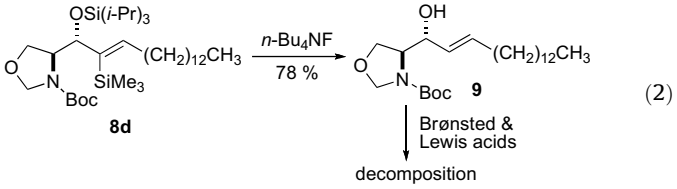
With an efficient procedure now in hand for the preparation of a suitably protected α-amino-β-alkoxy aldehyde with the desired 15-carbon alkyne, we next attempted the conversion of the coupling product **8d** to D-*erythro*-sphingosine. Exhaustive desilylation of **8d** with *n*-Bu_4NF proceeded cleanly to afford alkene **9** in 78% yield (Eq. 2). However, all attempts to deprotect the aminoalcohol of **9** were unsuccessful. A broad range of Lewis acids and Brønsted acids led to extensive decomposition, with at best only trace quantities of sphingosine being observed.

Table 2
Additions to aldehyde **9**



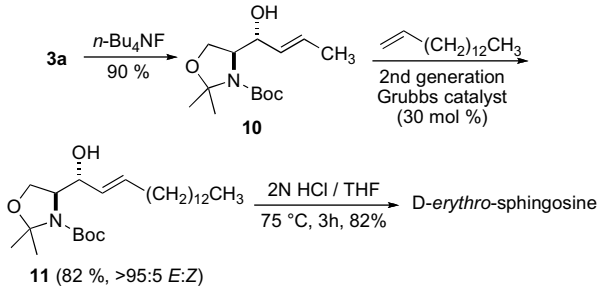
7 **2a-d** **8a-d**

Entry	R	Product (yield)	dr
1	CH_3 (**2a**)	**8a** (80%)	>95:5
2	C_6H_5 (**2b**)	**8b** (80%)	>95:5
3	$(CH_2)_3CH_3$ (**2c**)	**8c** (78%)	>95:5
4	$(CH_2)_{12}CH_3$ (**2d**)	**8d** (78%)	>95:5



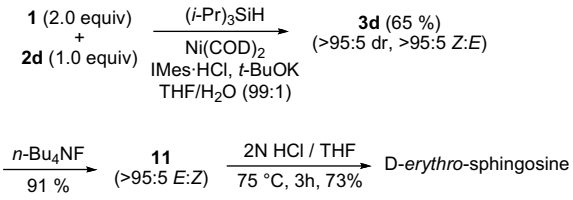
8d **9** (2)

Since the Garner aldehyde-derived products **3a–d** (Table 1) could all be cleanly deprotected, we opted to re-examine the studies with aldehyde **1** to avoid the inefficient deprotection of compound **9**. Desilylation of addition product **3a** (Table 1, entry 1) proceeded cleanly with *n*-Bu_4NF to afford alkene **10**, followed by cross metathesis[12] with 1-pentadecene (82% yield) to afford **11** and then 2 N HCl-mediated deprotection (82% yield) to afford D-*erythro*-sphingosine, which was indistinguishable from natural material (Scheme 3).



Scheme 3. Sphingosine synthesis by cross metathesis.

Although the above route involving a cross metathesis strategy starting from vinyl silane **3a** was relatively efficient, we were nonetheless troubled by the inefficiency of the more direct strategy involving coupling of Garner aldehyde **1** with silylalkyne **2d**. We therefore examined the reaction more extensively, and in analogy to an observation made in our recent synthesis of aigialomycin D,[13] we ultimately found that employing 2.0 equiv of Garner aldehyde **1** in couplings of **2d** with trace water in THF allowed reasonably efficient couplings,[14] providing the desired vinyl silane **3d** in 65% isolated yield with complete stereocontrol (>98:2 dr, >98:2 *Z*/*E*, Scheme 4). *n*-Bu_4NF-mediated deprotection of **3d** to **11** proceeded in 91% isolated yield, which was followed by the 2 N HCl deprotection described above (73% yield) to complete a more direct synthesis of D-*erythro*-sphingosine. This highly direct procedure thus allows the selective synthesis of D-*erythro*-sphingosine in three steps from Garner aldehyde **1**, without requiring the stoichiometric use of a vinyl organometallic reagent.



Scheme 4. Sphingosine synthesis using alkyne **2d**.

3. Summary and conclusions

The nickel-catalyzed reductive coupling of Garner aldehyde **1** with silylalkynes employing triisopropylsilane as reducing agent provides a direct and general strategy for the synthesis of unsaturated *anti*-1,2-aminoalcohols. Application of the procedure in a direct and efficient synthesis of D-*erythro*-sphingosine was illustrated (Scheme 4).

4. Experimental

4.1. General

Unless otherwise noted, all reactions were conducted in flame-dried glassware under a nitrogen atmosphere. THF was purified with an Innovative Technologies SPS-400 solvent system under nitrogen. $Ni(COD)_2$ (Strem Chemicals Inc., used as received), 1,3-dimesitylimidazolium chloride and *t*-BuOK (Acros, Fisher Scientific International Inc., used as received) were stored and weighed in an argon or nitrogen inert atmosphere glovebox. All alkynes (Sigma–Aldrich) were distilled or prepared and stored under nitrogen gas. All aldehydes were freshly prepared and flushed with nitrogen gas before using. Optical rotations were obtained on a Rudolph Autopol III polarimeter using a quartz cell with 1.0 mL capacity and 1 dm cell path length. Optical rotations were determined in $CHCl_3$, with concentration reported in units of 1 g/100 mL. ^1H and ^{13}C spectra were obtained in $CDCl_3$ or benzene-d_6 on a Varian Mercury 400 or Varian Unity 500 MHz instrument. Chemical shifts of ^1H NMR spectra were recorded in parts per million (ppm) on the δ scale from an internal standard of residual chloroform (7.27 ppm) or benzene (7.15 ppm). Chemical shifts of ^{13}C NMR spectra were recorded in parts per million from the central peak of $CDCl_3$ (77.0 ppm) or benzene-d_6 (128.0 ppm) on the δ scale. High resolution mass spectra (HRMS) were obtained on a VG-70-250-s spectrometer manufactured by Micromass Corp. (Manchester, UK) at the University of Michigan Mass Spectrometry Laboratory.

4.2. Trimethyl(pentadec-1-ynyl)silane (2d)

Pentadec-1-yne (624 mg, 3.0 mmol) was dissolved in THF (15 mL) and then cooled to −78 °C, followed by dropwise addition of *n*-BuLi (1.34 mL, 2.25 M in THF). The solution was allowed to warm to rt over 30 min, followed by cooling back to −78 °C. Trimethylsilylchloride (844 μL, 3.3 mmol) was then added dropwise to the solution. The mixture was allowed to warm to rt and was stirred for 10 min. The resulting colorless solution was quenched with saturated sodium bicarbonate solution and was extracted with diethyl ether three times. The combined organic layer was washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was distilled under vacuum (100 °C, 0.02 mmHg) to afford 780 mg (93%) of **2d** as a colorless oil. ^1H NMR (400 MHz, $CDCl_3$) δ 2.16 (t, J=7.2 Hz, 2H), 1.46 (m, 2H), 1.19–1.38 (m, 20H), 0.83 (t, J=7.2 Hz, 3H), 0.09 (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 107.8, 84.2, 31.9, 29.69, 29.66, 29.60, 29.5, 29.4, 29.1, 28.8, 28.6, 22.7, 19.8, 14.1, 0.2 (one peak is unresolved); IR (film) 2923, 2174 cm^{-1}; HRMS EI (m/z): $[M]^+$ calcd for $C_{18}H_{36}Si$ 280.2586; found 280.2598.

4.3. General procedure for Ni(0)-catalyzed reductive coupling reactions

THF (4.0 mL) was added to a solid mixture of 1,3-dimesitylimidazolium chloride (17.0 mg, 0.050 mmol), *t*-BuOK (6 mg, 0.05 mmol), and $Ni(COD)_2$ (14 mg, 0.05 mmol) at rt. The resulting solution was stirred for 5 min until the color turned dark blue. *i*-Pr_3SiH (2.0 equiv) was added, followed by addition of a THF solution (1.0 mL) of the aldehyde (0.50 mmol) and alkyne (0.60 mmol). The reaction mixture was stirred 1–4 h at rt until the aldehyde was consumed as judged by TLC analysis. The reaction mixture was quenched with saturated sodium bicarbonate solution and was extracted with diethyl ether three times. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified via flash chromatography (SiO_2) to afford the desired product.

*4.3.1. (S)-tert-Butyl 2,2-dimethyl-4-((S,E)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)but-2-enyl)oxazolidine-3-carboxylate (**3a**)*

Following the general procedure, aldehyde **1**[11] (114 mg, 0.50 mmol), trimethyl(prop-1-ynyl)silane (**2a**) (67 mg, 0.60 mmol), $Ni(COD)_2$ (14 mg, 0.05 mmol), 1,3-dimesitylimidazolium chloride (17 mg, 0.05 mmol), *t*-BuOK (6 mg, 0.05 mmol), and *i*-Pr_3SiH (158 mg, 1.0 mmol) gave, after column chromatography (1:49 ether/hexanes), 195 mg of (*S*)-*tert*-butyl 2,2-dimethyl-4-((*S*,*E*)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)but-2-enyl)oxazolidine-3-carboxylate (**3a**) (78%) as a colorless oil as a (>95:5) ratio of diastereomers. $[\alpha]_D^{24}$ −5.4 (*c* 7.65, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6, 80 °C) δ 6.57 (q, J=7.2 Hz, 1H), 5.22 (s, 1H), 4.25 (dd, J=5.6, 8.4 Hz, 1H), 3.97–4.00 (m, 1H), 3.72 (t, J=8.4 Hz, 1H), 1.70 (d, J=7.2 Hz, 3H), 1.67 (s, 3H), 1.50 (s, 3H), 1.41 (s, 9H), 1.10–1.20 (m, 21H), 0.32 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6, 80 °C) δ 153.4, 142.2, 137.7, 137.6, 95.2, 79.6, 73.8, 62.6, 62.1, 28.6, 27.2, 26.0, 18.6, 17.3, 13.6, 0.54; IR (film) 2944, 1693, 1615 cm^{-1}; HRMS ES (m/z): $[M+Na]^+$ calcd for $C_{26}H_{53}NNaO_4Si_2$ 522.3411; found 522.3391.

*4.3.2. (S)-tert-Butyl 2,2-dimethyl-4-((S,E)-3-phenyl-1-(triisopropylsilyloxy)-2-(trimethylsilyl)allyl)oxazolidine-3-carboxylate (**3b**)*

Following the general procedure, aldehyde **1** (114 mg, 0.50 mmol), 1-phenyl-2-(trimethylsilyl)acetylene (**2b**) (104 mg, 0.60 mmol), $Ni(COD)_2$ (14 mg, 0.05 mmol), 1,3-dimesitylimidazolium chloride (17 mg, 0.05 mmol), *t*-BuOK (6 mg, 0.05 mmol), and *i*-Pr_3SiH (158 mg, 1.0 mmol) gave, after column chromatography (2% ether/hexanes), 237 mg of (*S*)-*tert*-butyl 2,2-dimethyl-4-((*S*,*E*)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)but-2-enyl)oxazolidine-3-carboxylate (**3b**) (80%) as a light yellow oil as a (>95:5) ratio of diastereomers. $[\alpha]_D^{24}$ −1.5 (*c* 1.0, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6, 60 °C) δ 7.95 (s, 1H), 7.33–7.34 (m, 2H), 7.16–7.27 (m, 3H), 5.69 (s, 1H), 4.50 (dd, J=6.0, 8.8 Hz, 1H), 4.28–4.31 (m, 1H), 3.99 (dd, J=7.6, 8.8 Hz, 1H), 1.85 (s, 3H), 1.66 (s, 3H), 1.54 (s, 9H), 1.34–1.39 (m, 21H), 0.31 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6, 75 °C) δ 153.7, 145.7, 142.3, 142.2, 140.8, 128.8, 128.2, 127.3, 95.4, 79.8, 73.5, 62.3, 62.1, 28.6, 27.2, 26.0, 18.77, 18.72, 13.7, 1.0; IR (film) 2945,1691, 1592 cm^{-1}; HRMS ES (m/z): $[M+Na]^+$ calcd for $C_{31}H_{55}NNaO_4Si_2$ 584.3567; found 584.3572.

*4.3.3. (S)-tert-Butyl 2,2-dimethyl-4-((S,Z)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)hept-2-enyl)oxazolidine-3-carboxylate (**3c**)*

Following the general procedure, aldehyde **1** (259 mg, 1.0 mmol), hex-1-ynyltrimethylsilane (**2c**) (185 mg, 1.2 mmol), $Ni(COD)_2$ (28 mg, 0.10 mmol), 1,3-dimesitylimidazolium chloride (34 mg, 0.10 mmol), *t*-BuOK (11 mg, 0.10 mmol), and *i*-Pr_3SiH

(316 mg, 2.0 mmol) gave, after column chromatography (2% ether/hexanes), 352 mg of (*S*)-*tert*-butyl 2,2-dimethyl-4-((*S*,*Z*)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)hept-2-enyl)oxazolidine-3-carboxylate (**3c**) (68%) as a colorless oil as a (>95:5) ratio of diastereomers. ^{1}H NMR (400 MHz, C_6D_6, 80 °C) δ 6.57 (t, *J*=7.6 Hz, 1H), 5.30 (major rotamer isomer, br s, 0.85H), 5.18 (minor rotamer, br s, 0.15H), 4.27–4.34 (m, 1H), 4.03 (s, 1H), 3.78 (t, *J*=8.4 Hz, 1H), 2.10–2.23 (m, 2H), 1.70 (s, 3H), 1.69 (s, 3H), 1.52 (s, 3H), 1.42 (s, 9H), 1.27–1.44 (m, 4H), 1.14–1.22 (m, 21H), 0.87 (t, *J*=7.2 Hz, 3H), 0.36 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6, 80 °C) δ 153.5, 143.8, 140.8, 95.3, 79.6, 74.2, 62.7, 62.2, 32.3, 31.9, 28.6, 27.2, 26.2, 22.8, 18.7, 18.4, 13.9, 13.6, 0.78; IR (film) 2924, 1705 cm^{-1}; HRMS ES (*m*/*z*): [M+Na]$^+$ calcd for $C_{29}H_{59}NNaO_4Si_2$ 564.3880; found 564.3875.

4.3.4. (*S*)-tert-Butyl 4-((*S*,*E*)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)but-2-enyl)oxazolidine-3-carboxylate (**8a**)

Following the general procedure, (*S*)-*tert*-butyl 4-formyloxazolidine-3-carboxylate (**7**)[15] (100 mg, 0.50 mmol), trimethyl(prop-1-ynyl)silane (**2a**) (67 mg, 0.60 mmol), Ni(COD)$_2$ (14 mg, 0.05 mmol), 1,3-dimesitylimidazolium chloride (17 mg, 0.05 mmol), *t*-BuOK (6 mg, 0.05 mmol), and *i*-Pr$_3$SiH (158 mg, 1.0 mmol) gave, after column chromatography (2% ether/hexanes), 182 mg of (*S*)-*tert*-butyl 4-((*S*,*E*)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)but-2-enyl)oxazolidine-3-carboxylate (**8a**) (80%) as a colorless oil as a (>95:5) ratio of diastereomers. ^{1}H NMR (400 MHz, C_6D_6, 75 °C) δ 6.62 (qd, *J*=7.2, 1.2 Hz, 1H), 5.22 (br s, 1H), 5.18 (s, 1H), 4.75 (d, *J*=4.4 Hz, 1H), 4.16 (dd, *J*=8.0, 7.2 Hz, 1H), 3.99 (td, *J*=7.2, 2.4 Hz, 1H), 3.75 (t, *J*=8.0 Hz, 1H), 1.67 (dd, *J*=7.2, 1.2 Hz, 3H), 1.41 (s, 9H), 1.12–1.14 (m, 21H), 0.27 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6, 75 °C) δ 154.0, 141.2, 137.4, 80.8, 79.9, 73.4, 73.2, 66.2, 60.1, 28.5, 18.44, 18.39, 17.2, 13.29, 13.27, 0.13;IR (film) 2944, 2867, 1705, 1616 cm^{-1}; HRMS ES (*m*/*z*): [M+Na]$^+$ calcd for $C_{24}H_{49}NNaO_4Si_2$ 494.3098; found 494.3100.

4.3.5. (*S*)-tert-Butyl 4-((*S*,*E*)-3-phenyl-1-(triisopropylsilyloxy)-2-(trimethylsilyl)allyl)oxazolidine-3-carboxylate (**8b**)

Following the general procedure, (*S*)-*tert*-butyl 4-formyloxazolidine-3-carboxylate (**7**) (100 mg, 0.50 mmol), 1-phenyl-2-(trimethylsilyl)acetylene (**2b**) (104 mg, 0.60 mmol), Ni(COD)$_2$ (14 mg, 0.05 mmol), 1,3-dimesitylimidazolium chloride (17 mg, 0.05 mmol), *t*-BuOK (6 mg, 0.05 mmol), and *i*-Pr$_3$SiH (158 mg, 1.0 mmol) gave, after column chromatography (2% ether/hexanes), 213 mg of (*S*)-*tert*-butyl 4-((*S*,*E*)-3-phenyl-1-(triisopropylsilyloxy)-2-(trimethylsilyl)allyl)oxazolidine-3-carboxylate (**8b**) (80%) as a light yellow oil as a (>95:5) ratio of diastereomers. ^{1}H NMR (400 MHz, C_6D_6, 75 °C) δ 7.81 (s, 1H), 7.03–7.17 (m, 5H), 5.44 (s, 1H), 5.24 (s, 1H), 4.77 (d, *J*=4.0 Hz, 1H), 4.25 (t, *J*=7.6, 1.6 Hz, 1H), 4.16 (dt, *J*=1.6, 7.6 Hz, 1H), 3.91 (t, *J*=7.6 Hz, 1H), 1.42 (s, 9H), 1.82–1.90 (m, 21H), 0.12 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6, 75 °C) δ 154.1, 144.6, 142.1, 140.7, 128.7, 128.2, 127.3, 80.9, 80.1, 73.84, 73.76, 66.1, 60.0, 28.6, 18.6, 18.5, 13.41, 13.43, 0.73; IR (film) 2944, 2867, 1702 cm^{-1}; HRMS ES (*m*/*z*): [M+Na]$^+$ calcd for $C_{29}H_{51}NNaO_4Si_2$ 556.3254; found 556.3249.

4.3.6. (*S*)-tert-Butyl 4-((*S*,*Z*)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)hept-2-enyl)oxazolidine-3-carboxylate (**8c**)

Following the general procedure, (*S*)-*tert*-butyl 4-formyloxazolidine-3-carboxylate (**7**) (100 mg, 0.50 mmol), hex-1-ynyltrimethylsilane (**2c**) (92 mg, 0.60 mmol), Ni(COD)$_2$ (14 mg, 0.50 mmol), 1,3-dimesitylimidazolium chloride (14 mg, 0.10 mmol), *t*-BuOK (6 mg, 0.50 mmol), and *i*-Pr$_3$SiH (158 mg, 1.0 mmol) gave, after column chromatography (2% ether/hexanes), 200 mg of (*S*)-*tert*-butyl 4-((*S*,*Z*)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)hept-2-enyl)-oxazolidine-3-carboxylate (**8c**) (78%) as a colorless oil as a (>95:5) ratio of diastereomers. ^{1}H NMR (400 MHz, C_6D_6) δ 6.57 (t, *J*=7.2 Hz, 1H), 5.25 (br s, 2H), 4.75 (d, *J*=4.0 Hz, 1H), 4.21 (t, *J*=7.6 Hz, 1H), 4.00–4.10 (m, 1H), 3.84 (t, *J*=7.6 Hz, 1H), 2.00–2.18 (m, 2H), 1.39 (s, 9H), 1.21–1.32 (m, 4H), 1.04–1.17 (m, 21H), 0.84 (t, *J*=7.2 Hz, 3H), 0.29 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6, 75 °C) δ 154.0, 143.5, 139.8, 80.9, 79.9, 73.3, 66.2, 60.0, 32.3, 31.9, 28.6, 22.8, 18.52, 18.50, 13.9, 13.3, 0.42; IR (film) 2945, 1705 cm^{-1}; HRMS ES (*m*/*z*): [M+Na]$^+$ calcd for $C_{27}H_{55}NNaO_4Si_2$ 536.3567; found 536.3572.

4.3.7. (*S*)-tert-Butyl 4-((*S*,*Z*)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)hexadec-2-enyl)oxazolidine-3-carboxylate (**8d**)

Following the general procedure, (*S*)-*tert*-butyl 4-formyloxazolidine-3-carboxylate (**7**) (100 mg, 0.50 mmol), trimethyl(pentadec-1-ynyl)silane (**2d**) (168 mg, 0.60 mmol), Ni(COD)$_2$ (14 mg, 0.50 mmol), 1,3-dimesitylimidazolium chloride (14 mg, 0.10 mmol), *t*-BuOK (6 mg, 0.50 mmol), and *i*-Pr$_3$SiH (158 mg, 1.0 mmol) gave, after column chromatography (2% ether/hexanes), 249 mg of (*S*)-*tert*-butyl 4-((*S*,*Z*)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)hept-2-enyl)oxazolidine-3-carboxylate (**8d**) (78%) as a colorless oil as a (>95:5) ratio of diastereomers. ^{1}H NMR (400 MHz, C_6D_6, 75 °C) δ 6.23 (t, *J*=7.2 Hz, 1H), 5.23 (s, 2H), 4.75 (d, *J*=4.0 Hz, 1H), 4.23 (t, *J*=7.6 Hz, 1H), 4.03 (t, *J*=7.2 Hz, 1H), 3.83 (t, *J*=8.0 Hz, 1H), 2.11–2.29 (m, 2H), 1.41 (s, 9H), 1.27–1.38 (m, 22H), 1.12–1.18 (m, 21H), 0.90 (t, *J*=7.2 Hz, 3H), 0.30 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6, 75 °C) δ 153.5, 143.5, 139.8, 80.9, 79.9, 73.2, 66.2, 60.1, 32.2, 30.2, 30.1, 30.0, 29.9, 29.8, 29.7, 28.6, 23.0, 18.54, 18.48, 14.1, 13.3, 0.44; IR (film) 2925, 1705, 1612 cm^{-1}; HRMS ES (*m*/*z*): [M+Na]$^+$ calcd for $C_{36}H_{73}NNaO_2Si_2$ 662.4976; found 642.4979.

4.4. Synthesis of D-*erythro*-sphingosine from compound 3a (Scheme 3)

4.4.1. (*S*)-tert-Butyl 4-((*R*,*E*)-1-hydroxybut-2-enyl)-2,2-dimethyloxazolidine-3-carboxylate (**10**)

n-Bu$_4$NF (15.0 mL of 1.0 M in THF, 10.0 equiv) was added to dissolve (*S*)-*tert*-butyl 2,2-dimethyl-4-((*S*,*E*)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)but-2-enyl)oxazolidine-3-carboxylate (**3a**) (750 mg, 1.5 mmol) at rt. The solution was stirred for 12 h at rt, and the mixture was quenched with saturated sodium bicarbonate and extracted with ethyl acetate three times. The combined organic layers were washed with brine and dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified via flash column chromatography (30% ether/hexanes) to afford 369 mg of (*S*)-*tert*-butyl 4-((*R*,*E*)-1-hydroxybut-2-enyl)-2,2-dimethyloxazolidine-3-carboxylate (**10**) (91%) as a colorless oil. ^{1}H NMR (400 MHz, C_6D_6, 75 °C) δ 5.57 (dq, *J*=15.2, 6.4 Hz, 1H), 5.42 (dd, *J*=15.2, 6.0 Hz, 1H), 4.21–4.28 (m, 1H), 3.86–3.96 (m, 1H), 3.74–3.82 (m, 1H), 3.64 (dd, *J*=8.8, 6.8 Hz, 1H), 3.00 (v. br s, 1H), 1.61 (s, 3H), 1.55 (d, *J*=6.4 Hz, 3H), 1.45 (s, 3H), 1.37 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6, 75 °C) δ 131.7, 126.8, 94.5, 80.0, 73.7, 64.9, 62.7, 28.4, 26.8, 24.4, 17.6; IR (film) 3432, 2923, 1703 cm^{-1}; HRMS ES (*m*/*z*): [M+Na]$^+$ calcd for $C_{14}H_{25}NNaO_4$ 294.1681; found 294.1676.

4.4.2. (*S*)-tert-Butyl 4-((*R*,*E*)-1-hydroxyhexadec-2-enyl)-2,2-dimethyloxazolidine-3-carboxylate (**11**)

Dichloromethane was added to dissolved (*S*)-*tert*-butyl 4-((*R*,*E*)-1-hydroxybut-2-enyl)-2,2-dimethyloxazolidine-3-carboxylate (**10**) (85 mg, 0.40 mmol) and pentadec-1-ene (170 mg, 0.80 mmol). Second generation Grubbs catalyst (33 mg, 0.04 mmol) was added to the solution and the reaction mixture was heated at reflux for 2 h. Additional pentadec-1-ene (170 mg, 0.80 mmol) and second generation Grubbs catalyst (33 mg, 0.04 mmol) were then added. After another 4 h, more second generation Grubbs catalyst (33 mg, 0.04 mmol) was added. The mixture was then concentrated, and the residue was purified via flash chromatography (30% ether/hexanes) to provide 144 mg of (*S*)-*tert*-butyl 4-((*R*,*E*)-1-hydroxyhexadec-2-enyl)-2,2-dimethyloxazolidine-3-carboxylate (**11**) (82%) as a colorless oil. ^{1}H NMR data (400 MHz, C_6D_6, 60 °C) were identical to that previously reported.[10a]

4.4.3. D-erythro-Sphingosine

(*S*)-*tert*-Butyl-4-((*R*,*E*)-1-hydroxyhexadec-2-enyl)-2,2-dimethyloxazolidine-3-carboxylate (**11**) (100 mg, 0.23 mmol) was dissolved in THF (1.0 mL) and 2 N HCl (1.0 mL), and the reaction mixture was stirred at 75 °C for 12 h. THF was removed in vacuo, and the less polar impurities were extracted with ether/hexanes (1:1, 10 mL). The aqueous layer was basified with 2 N NaOH to pH 12 and extracted with dichloromethane. The combined organic layers were washed with brine, dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified via flash chromatography (SiO_2) eluting with $CHCl_3$/MeOH/NH_4OH (130:25:4) to afford 56 mg of **1** (0.19 mmol, 82% yield) as a white solid. Mp=73–74 °C; $[\alpha]_D^{24}$ −1.0 (*c* 0.45, $CHCl_3$). ^1H NMR data (500 MHz, $CDCl_3$) were identical with that previously reported.[10a,i]

4.5. Synthesis of D-*erythro*-sphingosine from compound 3d (Scheme 4)

*4.5.1. (S)-tert-Butyl 2,2-dimethyl-4-((S,E)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)hexadec-2-enyl)oxazolidine-3-carboxylate (**3d**)*

A modification of the general procedure was followed: 30 μL of water was added immediately after the addition of the aldehyde and alkyne. Garner aldehyde **1** (92 mg, 0.4 mmol), trimethyl(pentadec-1-ynyl)silane (**2d**) (56 mg, 0.2 mmol), 1,3-dimesitylimidazolium chloride (7.0 mg, 0.02 mmol), *t*-BuOK (2 mg, 0.02 mmol) and $Ni(COD)_2$ (6 mg, 0.02 mmol), *i*-Pr_3SiH (63 mg, 0.4 mmol), and water (30 μL) gave, after column chromatography (2% ether/hexanes), 87 mg of (*S*)-*tert*-butyl 2,2-dimethyl-4-((*S*,*E*)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)hexadec-2-enyl)oxazolidine-3-carboxylate (**3d**) (65%) as a colorless oil (>95:5 dr). $[\alpha]_D^{24}$ −4.0 (*c* 2.30, $CHCl_3$). ^1H NMR (400 MHz, C_6D_6, 75 °C) δ 6.58 (t, *J*=7.6 Hz, 1H), 5.30 (br s, 1H), 4.32 (dd, *J*=5.6, 8.8 Hz, 1H), 4.00–4.04 (m, 1H), 3.78 (t, *J*=8.4 Hz, 1H), 2.16–2.26 (m, 2H), 1.68 (s, 3H), 1.50 (s, 3H), 1.40 (s, 9H), 1.25–1.35 (m, 22H), 1.18–1.20 (m, 21H), 0.87 (t, *J*=6.8 Hz, 3H), 0.35 (s, 9H); ^{13}C NMR (100 MHz, C_6D_6, 80 °C) δ 153.5, 143.9, 143.8, 140.9, 95.3, 79.6, 73.8, 62.7, 62.2, 32.3, 30.3, 30.2, 30.01, 30.00, 29.9, 29.7, 28.6, 27.2, 26.2, 23.0, 18.7, 13.6, 0.81; IR (film) 2924, 2854, 1693 cm^{-1}; HRMS ES (*m*/*z*): $[M+Na]^+$ calcd for $C_{38}H_{77}NNaO_4Si$ 690.5289; found 690.5298.

*4.5.2. (S)-tert-Butyl 4-((R,E)-1-hydroxyhexadec-2-enyl)-2,2-dimethyloxazolidine-3-carboxylate (**11**)*

n-Bu_4NF (0.5 mL of 1.0 M in THF, 10.0 equiv) was added to dissolve (*S*)-*tert*-butyl 2,2-dimethyl-4-((*S*,*E*)-1-(triisopropylsilyloxy)-2-(trimethylsilyl)hexadec-2-enyl)oxazolidine-3-carboxylate (**3d**) (35 mg, 0.05 mmol) at rt. The solution was stirred for 12 h at rt. The mixture was quenched with saturated sodium bicarbonate and extracted with ethyl acetate (10 mL) three times. The combined organic layers were washed with brine and dried over magnesium sulfate, filtered, and concentrated in vacuo. The residue was purified via flash chromatography (30% ether/hexanes) to afford 34 mg of (*S*)-*tert*-butyl 4-((*R*,*E*)-1-hydroxyhexadec-2-enyl)-2,2-dimethyloxazolidine-3-carboxylate (**11**) (91%) as a colorless oil. $[\alpha]_D^{24}$ −28 (*c* 0.65, $CHCl_3$). ^1H NMR data (400 MHz, C_6D_6, 60 °C) and optical rotation data were identical to that previously reported.[10a]

4.5.3. D-erythro-Sphingosine

The identical procedure to that described above (Section 4.4.3) was performed using **11** (50 mg, 0.11 mmol) to afford 24 mg of D-*erythro*-sphingosine **1** (0.080 mmol, 73% yield).

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